REMARKS

This amendment is being filed in response to the Office Action mailed August 11, 2003. Applicants thank the Examiner for renumbering claims 28 to 39, submitted by Amendment filed May 19, 2003, as claims 36 to 47. Accordingly, claims 1 to 12 and 36 to 47 are under consideration.

Regarding the Amendments

The amendments to the claims were made to address an informality. In particular, claims 38 to 42 have been amended to depend from claims 36 or 37 instead of claims 28 or 29 due to the renumbering of the claims submitted in the Amendment filed May 19, 2003. Thus, as the amendments to the claims were made to address an informality no new matter has been added. Accordingly, entry of the amendments is respectfully requested.

I. REJECTIONS UNDER 35 U.S.C. §112

The rejection of claims 1 to 12 and 36 to 47 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description is respectfully traversed. The Examiner states that allegedly Applicants have not provided an adequate written description of "inactive galectin-3 proteins....which can bind to the galectin-3 receptor, but which do not modulate cell migration," or "antibodies....which can lead to the formation of galectin oligomers." In particular, in respect to inactive galectin-3 proteins allegedly "Applicants have not disclosed which residues could be altered to allow for binding of galectin-3 to the receptor, but wherein said receptor does not cause migration." [Office Action at page 3, B., second paragraph]

Applicants first request clarification of the statement in the Office Action at page 3, B., second paragraph. In particular, the statement "Applicants have argued that inactive galectin-3 proteins can be made which can bind to the galectin-3 receptor, but which *do not* modulate cell migration." [Emphasis added] Applicants believe that the word "not" is a typographical error since Applicants argued in the Amendment filed May 19, 2003, that "a modified inactive galectin-3 that binds to a galectin-3 receptor but does not stimulate migration can inhibit binding of endogenous galectin-3 thereby *inhibiting* migration." [Emphasis added; see Amendment filed

May 19, 2003, page 9, second paragraph] Thus, Applicants' position is that a modified galectin-3 can inhibit migration.

To satisfy the written description requirement, an applicant "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Under the Guidelines for Determining Compliance with the Written Description Requirement, possession may be shown in a variety of ways including describing distinguishing identifying characteristics. M.P.E.P. §2163.02. Here, claims 1 to 12 and 36 to 47 are adequately described such that one skilled in the art would recognize that Applicants' were in possession of the invention claimed.

As set forth in Applicants previously filed Amendment, the structure of galectin-3 was known in the art at the time of the invention. As evidence of this knowledge, Exhibits A-C (Barondes *et al.*, J. Biol. Chem. 269:20807 (1994); Robertson *et al.*, Biochem. 29:8093 (1990); and Cherayil *et al.*, Proc. Natl. Acad. Sci. USA 87:7324 (1990), respectively) were previously submitted with the Amendment. Exhibit A describes the location of various domains important for function. In particular, the carbohydrate (CHO) binding domain (lectin domain), which mediates binding to receptor, is located in C-terminal region of the galectin-3 molecule. [see, for example, page 20808, Figure 2, dots]. Deletion of this region impairs activity. [see, for example, page 20807, column 2, first paragraph] The N-terminal half of galectin-3 mediates multimerization. [see, for example, page 20807, column 2, second full paragraph] Thus, in view of the knowledge in the art, one skilled in the art would know various galectin-3 functional domains, and that a CHO binding galectin-3 fragment lacking a functional multimerization domain would bind receptor but fail to multimerize.

As to particular examples of inactive galectin-3 proteins that inhibit migration, Applicants' respectfully direct the Examiner's attention to the specification which discloses that a modified galectin-3, a C-terminal galectin-3 fragment, inhibited monocyte migration induced by full-length galectin-3 (page 32, lines 7-16). These results therefore indicate that a galectin-3 fragment retaining the lectin domain and lacking the multimerization domain 1) does not itself stimulate cell migration and 2) can inhibit cell migration induced by native galectin-3. Although not bound by any particular theory, presumably this galectin-3 fragment interferes with full-length galectin-3 binding to galectin-3 receptor. Thus, in view of the specification, one skilled in

the art would know that galectin-3 fragments lacking functional multimerization domain but retaining CHO binding are inactive and can be used to inhibit migration.

As to particular examples of galectin-3 antibodies that lead to the formation of galectin oligomers, Applicants first wish to point out that this mechanism was merely provided as an example of how an antibody that binds galectin-3 could stimulate cell migration. Applicants emphasize that antibodies that bind galectin-3 and modulate cell migration may function by other mechanisms. Furthermore, the claims do not require that the antibody function by any particular mechanism. Rather, the claims (e.g., claims 36 to 47) merely require that migration be modulated using a galectin-3 binding polypeptide or a galectin-3 receptor binding polypeptide.

Evidence of galectin-3 antibodies that modulate migration is described in Liu *et al.* (Biochemistry 35:6073 (1996)), submitted herewith as Exhibit 1. The authors of Exhibit 1 describe generating and characterizing seven monoclonal antibodies that bind galectin-3 (see abstract and page 6076, Table 1). Three antibodies, A3A12, B3A12 and C1C2 potentiated galectin-3 binding to IgE (page 6076, second column, first full paragraph). Most of the seven antibodies also potentiated galectin-3 hemagluttinating activity, with A3A12 providing the greatest enhancement of activity (page 6077, paragraph bridging first and second columns). Finally, A3A12 significantly enhanced superoxide (SO) production of neutrophils (see page 6078, first column, first full paragraph and Figure 5). Thus, antibodies that bind galectin-3 and that stimulate galectin-3 activity were known at the time of the invention, as evidenced by Exhibit 1.

Although no data is presented in Exhibit 1 directly demonstrating that the antibodies induce galectin-3 oligomers, the authors of Exhibit 1 state that the potentiating activities are probably related to dimerization or oligomerization of galectin-3 through intermolecular interactions involving the amino-terminal domain, which increases avidity for receptor (see, for example, page 6078, paragraph bridging columns 1 and 2; see, also, the specification at page 10, lines 13-20). Corroborating evidence of galectin-3 oligomerization is that an Fab' fragment of antibody A3A12 did not enhance galectin-3 binding, indicating that enhancement of galectin-3 activity is attributable to divalence of the A3A12 antibody (Exhibit 1, the sentence bridging pages 6076 and 6077). Furthermore, Applicants reiterate that the recited antibodies are not bound by any particular mechanism of action. In any event, Exhibit 1 indicates that antibodies to galectin-3 that enhance galectin-3 activity exist.

Given that galectin-3 activity is enhanced by galectin-3 antibodies, these antibodies can therefore stimulate cell migration mediated by galectin-3. In support of this position, submitted herewith as Exhibit 2 is a sworn Declaration under 37 C.F.R. §1.132 by Dr. Liu, the inventor of the subject application. In Exhibit 2, Dr. Liu states that he is the first author of Exhibit 1 and has an intimate understanding of the data presented in Exhibit 1 (Exhibit 2, paragraphs 6 and 7). Dr. Liu concludes that based upon the studies described in Exhibit 1 and his expertise in the relevant art, that one or more of the antibodies described in Exhibit 1 is expected to stimulate cell migration as claimed (Exhibit 2, paragraph 9). Thus, given that antibodies that bind galectin-3 and stimulate galectin-3 activity and, therefore, cell migration exist, an adequate written description for such galectin-3 antibodies is provided.

In sum, in view of the fact that galectin-3 fragments that inhibit cell migration are disclosed in the specification, as exemplified by the C-terminal galectin-3 fragment, and that galectin-3 antibodies that stimulate galectin-3 activity and therefore stimulate cell migration exist, those skilled in the art would recognize galectin-3 fragments and galectin-3 antibodies having cell migration inhibiting and stimulating activity, respectively. As such, an adequate written description for galectin-3 proteins that inhibit cell migration and for galectin-3 antibodies that stimulate cell migration is provided, and the rejection of claims 1 to 12 and 36 to 47 under 35 U.S.C. §112, first paragraph must properly be withdrawn.

The rejection of claims 5, 6 and 40 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Examiner acknowledges that the specification is "enabling for methods modulating migration of cells expressing a galectin-3 receptor by using galectin-3, N- or C-terminal subsequences thereof, as well as galectin- binding polypeptides and galectin-3 receptor-binding polypeptides (e.g., antibodies)." However, allegedly the specification does not adequately enable "use of any and all 'subsequences' or 'fragments' of galectin-3." [Office Action at page 4, A.]

Claims 5, 6 and 40 are adequately enabled by the specification. The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. As stated by the Federal Circuit, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in

question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988)

Here, the specification discloses routine assays for identifying galectin-3 fragments/subsequences having the requisite activity. For example, the specification discloses both *in vitro* and *in vivo* cell migration assays (see, page 28, line 3, to page 29, line 6). The specification exemplifies these assays for intact galectin-3, C-terminal galectin-3 fragment and a galectin-3 antibody, B2C10 (page 29, line 22, to page 32, line 16; and page 34, line 18, to page 36, line 2). Thus, in view of the fact that the specification discloses routine assays for identifying galectin-3 fragments/subsequences that modulate cell migration *in vitro* and *in vivo*, one skilled in the art could obtain such galectin-3 fragments/subsequences without undue experimentation.

Furthermore, Applicants respectfully point out that "any and all" subsequences or fragments of galectin-3 need not be enabled because all galectin-3 subsequences/fragments are not included. Rather, only galectin-3 subsequences/fragments that modulate cell migration are included as subsequences/fragments. In this regard, as discussed above the specification discloses that both N-terminal and C-terminal domains of galectin-3 are important for galectin-3 activity (see, for example, page 10, lines 22-25; see, also, page 15, lines 11-13). In particular, the specification exemplifies a C-terminal galectin-3 fragment having a functional lectin domain that inhibits galectin-3 induced cell migration (page 32, lines 7-16). The domains conferring particular galectin-3 functions were also known in the art, as discussed above and of record.

In view of the teaching in the specification and knowledge in the art regarding galectin-3 structure and function, one skilled in the art would know how to obtain additional galectin-3 fragments/subsequences that modulate cell migration without undue experimentation. For example, to produce a galectin-3 subsequence that inhibits cell migration, the skilled artisan would know to delete all or a part of the N-terminal multimerization domain and to retain a functional lectin domain. To produce a galectin-3 subsequence that stimulates cell migration, the skilled artisan would know to delete amino acids outside of the lectin and multimerization domains in order to maintain activity. Thus, as the skilled artisan would know the galectin-3 sequences that may be deleted or retained in order to produce galectin-3 subsequences/fragments that stimulate or inhibit cell migration such galectin-3 subsequences/fragments could readily be produced without undue experimentation.

In sum, in view of the guidance in the specification, the skilled artisan would know routine *in vitro* and *in vivo* screening assays for identifying galectin-3 fragments/subsequences that stimulate or inhibit cell migration. Furthermore, in view of the guidance in the specification and knowledge in the art, the skilled artisan would also know regions of galectin-3 that could be deleted or mutated to produce galectin-3 subsequences/fragments that stimulate or inhibit cell migration. Thus, additional galectin-3 subsequences/fragments that stimulate or inhibit cell migration could be obtained without undue experimentation. As such, claims 5, 6 and 40 are adequately enabled and the rejection under 35 U.S.C. §112, first paragraph must properly be withdrawn.

The rejection of claims 1 to 12 and 36 to 47 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Examiner acknowledges that the specification is "enabling for methods of stimulating migration of cells expressing a galectin-3 receptor by using galectin-3, N- or C-terminal subsequences thereof, as well as inhibiting migration using galectin binding polypeptides and galectin-3 receptor-binding polypeptides (e.g., antibodies)." However, allegedly the specification does not adequately enable "inactive galectin-3 proteins or antibodies which oligomerize galectin-3 in order to stimulate migration" [Office Action at page 5, B.]

Claims 1 to 12 and 36 to 47 are adequately enabled by the specification. As discussed above, the specification discloses assays for identifying galectin-3 proteins, galectin-3 binding proteins and galectin-3 receptor binding proteins having the requisite activity. For example, the specification discloses *in vitro* and *in vivo* cell migration assays (see, page 28, line 3, to page 29, line 6). The specification exemplifies these assays for intact galectin-3, a C-terminal galectin-3 fragment and galectin-3 antibody, B2C10 (page 29, line 22, to page 32, line 16; and page 34, line 18, to page 36, line 2). Thus, because the specification discloses routine assays for identifying galectin-3 proteins, galectin-3 binding proteins and galectin-3 receptor binding proteins that modulate cell migration, the skilled artisan could readily obtain such molecules without undue experimentation.

Furthermore, as discussed above the specification discloses that both N-terminal and C-terminal domains of galectin-3 are important for galectin-3 activity (see, for example, page 10, lines 22-25; see, also, page 15, lines 11-13). The C-terminal lectin domain mediates CHO

binding (page 31, lines 17-18) and the specification exemplifies a C-terminal galectin-3 fragment that inhibits galectin-3 induced cell migration (page 32, lines 7-16). Moreover, as evidenced by previously submitted Exhibits A-C discussed above and in the record, the skilled artisan would know galectin-3 domains that confer particular functions. Thus, in view of the guidance in the specification and knowledge in the art, one skilled in the art would know how to produce additional inactive galectin-3 proteins that inhibit cell migration. For example, to produce an inactive galectin-3 that inhibits cell migration the skilled artisan would know to mutate or delete the N- terminal region of galectin-3 to destroy multimerization function but retain a functional lectin domain. Thus, the specification provides reasonable guidance for producing galectin-3 molecules that inhibit cell migration.

Regarding antibodies that "oligomerize galectin-3 in order to stimulate migration," as discussed above the recited antibodies are not bound by any mechanistic limitation. Furthermore, Exhibit 1 describes antibodies that bind to galectin-3 and enhance galectin-3 activity. Since these antibodies stimulate galectin-3 activity, it is expected that they will likewise stimulate cell migration (see Exhibit 2). Thus, Exhibit 1 describes galectin-3 antibodies that can be used to stimulate cell migration in accordance with the claimed methods.

In sum, in view of the guidance in the specification, the skilled artisan would know routine screening assays for identifying galectin-3 proteins that inhibit cell migration and antibodies that stimulate cell migration. Further in view of the specification and knowledge in the art, the skilled artisan would also know regions of galectin-3 that could be deleted or mutated to produce galectin-3 molecules that inhibit cell migration, as well as galectin-3 antibodies that stimulate migration. Thus, because galectin-3 proteins and galectin-3 antibodies that inhibit and stimulate cell migration, respectively, are available and, furthermore, could be produced without undue experimentation the claims are adequately enabled. As such, the rejection of claims 1 to 12 and 36 to 47 under 35 U.S.C. §112, first paragraph must properly be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 12 and 36 to 47 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

Date: 10-29-03

Robert M. Bedgood, Ph.D.
Reg. No. 43,488
Agent for Applicant

PILLSBURY WINTHROP LLP
11682 El Camino Real, Suite 200
San Diego, CA 92130-2593
Telephone: (858) 509-4093
Facsimile: (858) 509-4010